



European Society of Cardiology Working Group on Myocardial & Pericardial Diseases

Newsletter

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**Myocardial and
Pericardial Diseases**

ESC Working Group



EUROPEAN
SOCIETY OF
CARDIOLOGY®

Editorial News

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Dear Members of the Working Group,

Please find enclosed the 13th issue of our Newsletter.

In addition to the 'clinical case of the month' and the 'paper of the month' you will find within this issue the case resolution from the may case.

Best wishes for all of you.

S. Pauluvs

The paper of the month:

Genetic Evaluation of Cardiomyopathy. A Heart Failure Society of America Practice Guideline. R.E. Hershberger, J. Lindenfeld, L. Mestroni, C.E. Seidman, M.R.G. Taylor, and J.A. Towbin. J Cardiac Fail 2009;15:83-9

Presented by Prof. Claudio Rapezzi, Institute of Cardiology, University of Bologna and S. Orsola-Malpighi Hospital, Bologna,

This is the first available guideline document on genetic evaluation of patients with cardiomyopathy. Herein we summarize and comment the “strategy” of the document and the most relevant recommendations.

BACKGROUND AND AIMS

The authors acknowledge that the available clinical genetic data for each of the cardiomyopathies vary greatly in content and quality; consequently the quality and certainty of genetic counseling information is also variable. Whereas analytic validity of genetic tests (the ability of the test to detect a mutation) is attainable with current methods, clinical utility remains to be defined for all genetic testing of cardiomyopathies. In particular, a fundamental question remains to be answered: how will the genetic information, whether positive or negative, affect clinical decision-making for the patient or the patient’s family? The document contributes to clarify this topic. These guidelines do not address molecular testing in prenatal, newborn screening or in vitro fertilization settings.

METHODOLOGICAL APPROACH

This guideline organizes recommendations by six cardiac phenotypes

- Hypertrophic Cardiomyopathy (HCM),
- Dilated Cardiomyopathy (DCM),
- Arrhythmogenic Right Ventricular Dysplasia (ARVD),
- Restrictive Cardiomyopathy (RCM),
- Isolated Left Ventricular Noncompaction (LVNC),
- Cardiomyopathies associated with other extracardiac manifestations.

The authors acknowledge that “there is substantial overlap among phenotypes and some mutations are associated with more than one phenotype. However, therapeutic decision making is generally dictated by phenotype making this approach the most helpful for the clinician”. Whereas this approach is in line with the position statement on classification of the cardiomyopathies recently published by the Working Group on Myocardial and Pericardial Diseases from the European Society of Cardiology, only the classification document from the American Heart Association (based on a general nosographic approach) is considered and cited by the authors.

Very appropriately, the paper discusses the methodologic problems of the “levels of evidence” of the recommendations in the field of cardiomyopathies. Guidelines are generally based on randomized clinical trials and meta-analyses. However, because genetic testing is relatively new, randomized clinical trials demonstrating that performing the specific genetic test improves outcomes are not available.

Thus, these guidelines have used a different format for “level of evidence” that describes evidence for clinical validity that asks the question “Does the test correlate with the outcome of interest?” The hierarchy of types of evidence includes the following:

Level A: The specific genetic test or clinical test has a high correlation with the cardiomyopathic disease of interest in reasonably large studies from multiple centers.

Level B: The specific genetic test or clinical test has a high correlation with the cardiomyopathic disease of interest in small or single center studies.

Level C: The specific genetic test or clinical test correlates with the cardiomyopathic disease of interest in case reports.

RECOMMENDATIONS

The guideline document give recommendations on seven distinct aspects of the management of the patient with cardiomyopathy:

- Taking family history
- Clinical screening for cardiomyopathy in asymptomatic first-degree relatives
- Molecular Genetic Testing
- Genetic and family counseling
- Medical therapy
- Device therapies for arrhythmia and risk of sudden death,
- Referral to “tertiary” centers

Family history. “A careful family history for >3 generations is recommended for all patients with cardiomyopathy”.

The level of evidence of this recommendation is “A” for all the phenotypes except RCM for which it is “B”. Very appropriately, the guidelines underscore that family history is particularly relevant in the field of cardiomyopathies and is useful not only to family members but also to the proband since it enables physicians to reach a detailed diagnosis. Some general considerations and suggestions are given:

- When taking a family history, it is imperative that the professional recording it makes no a priori assumptions of which side of the family the disease originated¹⁰ and should consider bilineal inheritance (transmission of a disease-causing mutation in the same or a different gene from both mother and father)
- Construction of a pedigree is mandatory in order to ascertain the inheritance pattern. Pedigree analysis is undertaken to determine if the inheritance is autosomal dominant or recessive, X-linked dominant or recessive, or mitochondrial
- Expanding a family history beyond the 3rd generation and collecting medical data from relatives known or suspected to manifest clinical disease consistent with the cardiomyopathy in question can be enormously informative

Clinical screening for cardiomyopathy in asymptomatic first-degree relatives.

The guideline states that “**Clinical screening for cardiomyopathy in asymptomatic first-degree relatives is recommended**”. The level of evidence of this recommendation is “A” for all the phenotypes except RCM and LVNC for which it is “B”.

The guideline also takes into consideration the details of the first examination and of the follow-up visits.

"It is recommended (Level of Evidence = B) that clinical screening consist of:

- **History (with special attention to heart failure symptoms, arrhythmias, presyncope, and syncope)**
- **Physical examination (with special attention to the cardiac and skeletal muscle systems)**
- **Electrocardiogram**
- **Echocardiogram**
- **CK-MM (at initial evaluation only)**
- **Signal-averaged electrocardiogram (SAECG) in ARVD only**
- **Holter monitoring in HCM, ARVD**
- **Exercise treadmill testing in HCM**
- **Magnetic resonance imaging in ARVD"**

The following time intervals for follow-up visits are proposed:

Cardiomyopathy Phenotype	Interval if genetic testing is negative and/or if clinical family screening is negative	Screening interval if a mutation is present	Level of Evidence
HCM	Every 3 years until 30 years of age, except yearly during puberty; after 30 years, if symptoms develop.	Every 3 years until 30 years of age, except yearly during puberty; every 5 years thereafter	B
DCM	Every 3-5 years beginning in childhood.	Yearly in childhood; every 1-3 years in adults.	B
ARVD	Every 3-5 years after age 10.	Yearly after age 10 to 50 years of age	C
LVNC	Every 3 years beginning in childhood	Yearly in childhood; every 1-3 years in adults.	C
RCM	Every 3-5 years beginning in adulthood	Yearly in childhood; every 1-3 years in adults.	C

"Regardless of genotype, at-risk first-degree relatives with any abnormal clinical screening tests should be considered for repeat clinical screening at 1 year (Level of Evidence =C)."

The basis for all these extensive clinical screening recommendations is because cardiomyopathies (in contrast with many other genetic diseases) can be treated in almost all cases improving survival and/or enhancing quality of life.

Molecular Genetic Testing. *"Genetic testing should be considered for the one most clearly affected person in a family to facilitate family screening and management".* The level of evidence of this recommendation is "A" for HCM, RVAD and for cardiomyopathies associated with other extracardiac manifestations, is "B" for DCM and "C" for RCM and LVNC. The document give a list of specific genes which are available for screening according the cardiac phenotype. A single statement is dedicated to Fabry disease: **"Screening for Fabry disease is recommended in all men with sporadic or non-autosomal dominant (no male-to male)transmission of unexplained cardiac hypertrophy. (Level of Evidence = B)".**

As pointed out in the document, the main indication for genetic testing according this guideline is to facilitate family screening and management. Simply put, this guideline recognizes that at this time the primary value, and the primary reason to seek genetic testing for the genetic cardiomyopathies, is to more accurately predict the risk of a family member developing cardiomyopathy who at the present has little or no clinical evidence of cardiovascular disease. "If a disease-causing mutation is identified in the affected family member initially tested, and subsequent genetic testing of an at-risk but presymptomatic family member is negative, that family member's risk of developing the cardiomyopathy is substantially reduced. In this situation, the need for ongoing clinical screening in such a mutation negative family member is not recommended. On the other hand, if a disease-causing mutation is identified in an asymptomatic, at-risk family member, the confidence is much greater to infer risk for that individual. The individual should be counseled on the presenting signs and symptoms of the specific cardiomyopathy, the associated reduced penetrance and variable expressivity, and the rationale and frequency of the recommended clinical surveillance."

Notably, these recommendations are silent for any additional interventions specific for a disease-causing mutation. The reason for this stems from the lack of validated genotype-phenotype correlations of specific mutations with specific clinical cardiovascular outcomes. Unless or until specific mutations have been shown to reliably predict specific clinical outcomes (eg, increased or reduced risk of a specific event such as the development of symptomatic heart failure or the high probability of SCD), the recommendations will refer to the general behavior of each disease gene.

Genetic and family counselling

Genetic counseling is acknowledged as an essential component of the evaluation, diagnosis, and management of the cardiomyopathies. **" Genetic and family counseling is recommended for all patients and families with cardiomyopathy. (Level of Evidence = A)".**

According to the guideline, genetic counseling for the cardiomyopathies is undertaken by genetic counselors or geneticists who are knowledgeable of the cardiovascular clinical features of the type of cardiomyopathy in question, or by cardiologists who are expert in the cardiomyopathy in question and are fluent in the content and nature of genetic counseling for the patient and their family members. "Alliances of cardiologists with special interest and expertise in genetic cardiomyopathies with genetics professionals, are beginning to emerge."

Medical therapy. The finding of any specific mutation as the cause of the cardiomyopathy does not in itself guide therapy. Consequently, the general recommendation of the document is that **"medical therapy based on cardiac phenotype is recommended as outlined in the general guidelines. (Level of Evidence =A)"**. However, the characteristics associated with some disease genes can be integrated with the clinical and family data, and may appropriately impact all aspects of the clinical recommendations, including the frequency and stringency of presymptomatic screening for signs of disease, the strength of interventions to educate family members of risks and symptoms, the threshold for presymptomatic initiation of preventive or therapeutic interventions.

Device therapies for arrhythmias and risk of sudden death. As a general recommendation, the paper states that **"device therapies for arrhythmia and conduction system disease based on cardiac phenotype are recommended as outlined in the general guidelines. (Level of Evidence= B)"**. In particular, for DCM, a left ventricular ejection less than 30% to 35% is usually an indication for an ICD, regardless of etiology. However, a second recommendation (at an inferior level of evidence) is given by the guideline: **"In patients with cardiomyopathy and significant arrhythmia or known risk of arrhythmia an ICD may be considered before the left ventricular ejection fraction falls below 35%. (Level of Evidence = C)"**. This is the case when the **family history is positive for sudden cardiac death** (this concept is not developed in detail by the document) or for patients with **LMNA mutations**.

Referral to "tertiary" centers. **"Evaluation, genetic counseling, and genetic testing of cardiomyopathy patients are complex processes. Referral to centers expert in genetic evaluation and family-based management should be considered. (Level of Evidence =B)"**

The processes involved in clinical and genetic evaluation and testing for cardiomyopathies, are complex processes. Those practicing cardiovascular genetic medicine must remain up to date with the accelerating developments in the field, integrating clinical and genetic evaluations with genetic counseling. This includes knowledge of recent discoveries of mutations in genes not previously implicated in the cardiomyopathies, as well as emerging gene-phenotype and genotype-phenotype correlations. Complexity also results from the extensive locus (many genes) and allelic (many different mutations within those genes) heterogeneity. Advances in genetic testing technology are also leading to a proliferation of new genetic tests for the cardiomyopathies. Referral to a cardiovascular center specializing in genetic cardiomyopathy can assist in defining the appropriateness of genetic testing for all patients with all types of cardiomyopathy. Practitioners may also consider referral to cardiovascular genetics centers to promote the engagement of patients in research. Patient involvement is critical for continued discovery of unknown genes that cause cardiomyopathy, for establishing long-term natural history studies, and for harnessing this information to improve diagnosis and to improve treatments.

The clinical case of the month: *What is your diagnosis?*

Answers will be given in the next newsletter and on the web site

Presented by Dr. Pablo Garcia-Pavia and Dr. P. M. Elliott, Cardiomyopathy Unit, Heart Transplant Program, Puerta de Hierro University Hospital, Madrid, Spain and Inherited Cardiovascular Disease Unit, Department of Cardiology, The Heart Hospital, University College of London, London, UK.



Titel: “A 52 year old male with recurrent abdominal pain”

Case Presentation:

A 52 year old male with a previous history of hypertension and hypercholesterolaemia, presented to the emergency department of his local hospital with abdominal pain. He had undergone right and left carpal tunnel surgery five and three years previously. He had no family history of cardiac disease or sudden cardiac death. His mother had died from tuberculosis in her fifties and his father was 72 and asymptomatic. He had attended hospital several times during the previous 6 months always complaining of abdominal pain associated with nausea and sweating after meals. He was diagnosed with uncomplicated biliary colic but declined immediate surgical intervention.

Six months later, he represented after a collapse. His electrocardiogram demonstrated complete atrio-ventricular block. An urgent echocardiogram revealed “mild hypertrophy with normal ejection fraction”. A pacemaker was implanted and the patient was discharged on enalapril and simvastatin. Four months after pacemaker insertion he presented with shortness of breath and was still complaining of abdominal pain, asthenia and abdominal distension.

On physical examination his blood pressure was 95/65 mmHg and the jugular vein pressure was slightly raised with hepatic congestion and mild bilateral ankle oedema. The ECG and chest x-ray are presented in Figure 1. The patient was admitted for further investigations. An echocardiogram showed concentric left ventricular hypertrophy (15 mm), granular “sparkling” myocardium, mildly depressed left ventricular ejection fraction (50%) and biatrial enlargement (figure 2).

Figure 1a + b. ECG and Chest X-Ray

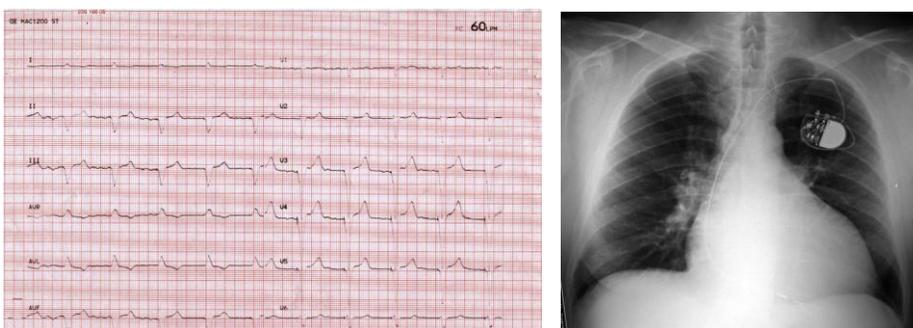
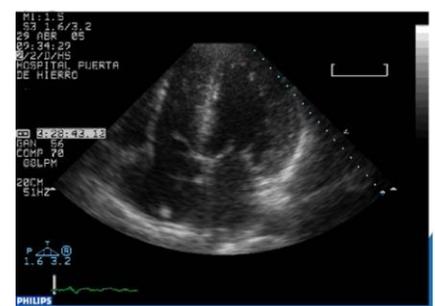


Figure 2: Echocardiography



What is your diagnosis?

Which further investigations would you perform?

Answer for the previous “Clinical case of the month” in May :

“Recurrent ACS in a Female Patient with Progressive Myocardial Dysfunction”

by Ewa Podolecka, MD, Zofia T. Bilinska, MD, PhD, Institute of Cardiology, Warsaw, Poland

General remarks:

Acute coronary syndromes (ACS) are most commonly associated with severe lesions in coronary arteries. Normal coronary arteries are found in 1-8.5% of ACS patients [1-3]. Only in one-third of these patients with normal coronary arteries could potential mechanisms leading to ACS be detected. They include vasomotion disorders, coagulation disorders, inflammation factors or emotional distress.

Celiac disease is a common autoimmune disease with estimates that the disease prevalence is up to 1% in the general population [4]. Celiac disease in children usually has the form of a malabsorption syndrome, but in adults, the manifestations may be scarce, and then it is harder to diagnose. Our 44-year-old female patient was diagnosed because of the physician's increased awareness of the co-occurrence of autoimmune diseases in patients with endocrine disorders, namely diabetes mellitus and hypothyroidism. The prevalence of celiac disease among patients with insulin-dependent diabetes mellitus and autoimmune thyroid disease has been reported to be between 2-5% [5].

Celiac disease results from permanent intolerance to gliadin, the main fraction of gluten. Gliadin, playing the role of antigen, forms immunological complexes in the intestinal mucosa, which results in mucosal inflammation, crypt hyperplasia and villous atrophy. The performance of IgA antibody testing, either with anti-endomysial or anti-tissue transglutaminase antibodies, is recommended for the diagnosis of celiac disease.

Although there are few case reports on an association between celiac disease and ACS [6,7], a population-based study did not show a higher prevalence of myocardial infarction in patients with celiac disease [8]. It may be linked with protective factors like lower serum cholesterol levels and lower blood pressure in patients with celiac disease [4,8].

Therefore, the presence of recurrent ACS with normal coronary angiography in our patient could mimic autoimmune myocarditis. In fact, celiac disease has been reported to appear with such comorbidities as autoimmunological myocarditis, dilated cardiomyopathy and heart failure [9-12]. Observed dyspneic episodes and recurrent pulmonary edema could be the result of the predominant left ventricle diastolic dysfunction in the patient with mild mitral incompetence. Co-occurrence of diabetes mellitus and thyroid disease could contribute to the clinical manifestation. Several studies have demonstrated evidence for left ventricular diastolic dysfunction in patients with diabetes mellitus independently of coronary artery disease [13,14]. Patients with hypothyroidism have a coronary endothelial dysfunction, which improves during l-thyroxin treatment [15,16].

In summary, in patients with recurrent unexplained ACS or heart failure symptoms who have normal coronary angiography and co-occurrence of diabetes mellitus and hypothyroidism, screening for celiac disease may be mandatory.

Question 1.

Do you think the patient should undergo endomyocardial biopsy? If she were your patient, would you do it?

Recurrent ACS is not an indication for endomyocardial biopsy [17]. However, in this patient, ACS could be a mask of recurrent “smoldering” autoimmune myocarditis. Furthermore, endomyocardial biopsy should be considered in patients with unexplained chronic heart failure and persistent cardiac dysfunction [18]. We have not performed the procedure, however, with last hospitalization, we were just about to do it, but with positive results of immunological studies we decided against doing endomyocardial biopsy in the patient.

Question 2.

Would you treat the patient with steroids ?

Recurrent ACSs in our patient subsided once gluten-free diet was introduced. The treatment effectiveness was confirmed by a significant anti-endomysial antibody titre drop (from 1:5120 to 1:40). A beneficial effect of gluten-free diet in patients with autoimmunological myocarditis and dilated cardiomyopathy has been reported before [10,11,19].

Introducing a gluten-free diet in our patient fully eliminated coronary manifestations, and in this way steroids were not considered at all. In one-year follow-up, also troponin was found to have normalized. This finding might suggest that eliminating one additional immunological factor in the patient already treated with statin and angiotensin convertase inhibitor resulted in a significant improvement in coronary microcirculation functioning.

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